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DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization Potential (81-6) TOX. CHEM NO: 603
(Guinea Pig)

MRID NO.: 425400-01 PC NO: 056301

TEST MATERIAL: Paranitrophenol, technical

SYNONYM/CAS NO.: 4-nitrophenol/000100-07-2

STUDY NUMBER: 75-51-0047-79-D

SPONSOR: U.S. Army Aviation and Troop Command, Natick Research, Development and Engineering Command, Natick, MA 01760-5020

TESTING FACILITY: U.S. Army Environmental Hygiene Agency, Toxicology Division, Aberdeen Proving Ground, MD 21010-5422

TITLE OF REPORT: Dermal Sensitization Guinea Pig Test

AUTHOR: Maurice H. Weeks

REPORT ISSUED: August 4, 1992 (reformatted report originally submitted August 21, 1979)

CONCLUSION:

Not a dermal sensitizer in guinea pigs (Draize method).

Core Classification: Unacceptable (not upgradable)

This study does not satisfy study guidelines for Dermal Sensitization (Series 81-6) and is not considered acceptable for regulatory purposes for the following reasons: significant differences from recommended Draize procedure (low challenge dose concentration, insufficient number of animals used), injection method not appropriate for detection of weak to moderate sensitizers (see "Discussion" for details).

Signed Quality Assurance and Good Laboratory Practice Statements were not present since this study was performed prior to enactment of GLP.

MATERIALS:

1. Test compound: Paranitrophenol, technical. Description - yellow-brown crystalline solid. Batch # - Lot 777A, 557735, N-20. Purity - 99.1%

2. Positive control compound: 1-chloro-2,4-dinitrobenzene (DCNB). Source, lot and purity not given. Solvent: propylene glycol.

3. Test animals: Species: Guinea Pig, male, Strain: Hartley albino, Age: young adult, Weight: 261 - 473 g at start of study, Source: Dutchland Farms, Denver, PA

4. Environment: Guinea pigs were housed individually in wire-bottom stainless steel cages and were quarantined for 2 weeks prior to initiation of treatment. Temperature: 21-25°C. Humidity: 40-60%. Light cycle 12 hr on/12 hr off. Food (not specified) and drinking water both administered ad libitum.

METHODS:

1. Primary Irritation Study: Guinea pigs were shaved and injected with either 0.05 or 0.10 ml 0.1% paranitrophenol solution in propylene glycol/saline in the right scapular (0.05 ml) and lumbosacral (0.1 ml) areas. Primary irritation of paranitrophenol was scored at 24 and 48 hrs after injection. Vehicle controls were injected into the corresponding left areas.

2. Dermal Sensitization Study: No reference for the test method was provided by the study authors but the protocol described was similar to the Draize method.

A 3% solution of paranitrophenol or the positive control substance DNCB was prepared in propylene glycol. A suspension in 0.9% saline was then prepared to give a final concentration of 0.1% paranitrophenol or DNCB. Animals were shaved over the scapular and lumbosacral regions. 0.05 ml of test compound solution and 0.05 ml of the vehicle were injected intradermally in the scapular regions (right and left, respectively) and skin reactions were graded as described below at 24 and 48 hrs.

A total of 9 additional sensitizing doses of 0.1 ml were injected at different sites on the dorsal lumbosacral area every other day (3X per 5-day week). Two weeks after the 9th injection, a challenge dose of 0.05 ml 0.1% paranitrophenol was injected into the lower right scapular area; vehicle was injected on the left side. Injection sites were scored for reaction at 24 and 48 hrs.

Negative cage controls (2 animals) were given only the initial injection of 0.05 ml 0.1% nitrophenol in the manner described above. Positive controls (2 animals) were given 0.05 ml of 0.1% DNCB in the manner described above. All cage controls were examined at 24 and 48 hrs for skin reaction. Guinea pigs were weighed immediately prior to initial dose and on Days 35 and 42.

3. Scoring of Skin Irritation/Sensitization: Edema, erythema and necrosis were scored and graded according to the grading system shown in the Appendix.

RESULTS AND DISCUSSION:

Paranitrophenol (0.1% in propylene glycol and saline; 0.1 ml injected intradermally) did not cause dermal sensitization and was not a primary irritant under the testing conditions reported in this study. In contrast, DCPN caused pronounced sensitization in all animals tested (data not shown in this review).

TB-I does not consider this study to be acceptable for regulatory purposes for several reasons. There were several significant changes in the procedure from the recommended protocol. The number of animals tested (10 per group) is less than the recommended number (20). The challenge dose (0.05 ml, 0.1% paranitrophenol) was also lower than recommended (1.0%). Secondly, although this study clearly identified a strong sensitizer like DCNB, the Draize method does not always identify weak to moderate dermal sensitizers and is not among the recommended methods in the Agency Guidelines for 81-6. Since dermal is probably a primary route of potential exposure to this compound, TB-I believes that a dermal sensitization potential study using a more sensitive method should be required.

In addition, the presentation of the data was in places unclear. In the 24 hr grading table (p. 13 of study report) there appears to be inconsistent notation of negative results (- vs no entry). Results of the irritation study were not included in the report.

Core-classification: Unacceptable (not upgradable)

APPENDIX

TABLE I. GRADING OF SKIN REACTIONS IN GUINEA PIG SENSITIZATION TEST

The grading system is designed so that the intensity of the skin reaction is represented by a proportionate numerical value and also any reaction elicited by the vehicle ("control substance") is subtracted from the reaction produced by the test substance and the vehicle combined.

The produce of the width and length (in mm) of the wheal is multiplied by the following reaction scores:

0 = needle puncture ("np") - no wheal
1 = very faint pink ("vfp") - no value is recorded for this reaction
2 = faint pink ("fp")
3 = pink ("p")
4 = red ("r")
5 = bright red ("R")
6 = edema = <1 mm in height ("e")
7 = edema = >1 mm in height ("E")
8* = necrosis = <1 sq mm ("nec")
9* = necrosis = >1 sq mm ("NEC")

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* The product of width and length of the necrotic area multiplied by 8 or 9 is added to the numerical value of any of the foregoing reactions that are present.

paranitrophenol
PC# 056301
TXChem # 603
MRID # 425400-01

81-6 Dermal Sensitization in the Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only)
2. — Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3. ✓ One of the following methods is utilized:
   - — Freund's complete adjuvant test
   - — Guinea pig maximization test
   - — Split adjuvant technique
   - — Buehler test
   - — Open epicutaneous test
   - — Maur optimization test
   - — Footpad technique in guinea pig
   - ✓ Other test accepted by OECD (specify) Draize / Landsteiner
4. ✓ Complete description of test
5. no Reference for test. not given but essentially same procedure as
6. — Test followed essentially as described in reference document.
7. ✓ Positive control included.

Differences from reference:

- 10 animals inst. of 20
- 0.1% challenge, not 1.0%

Criteria marked with a * are supplemental and may not be required for every study.